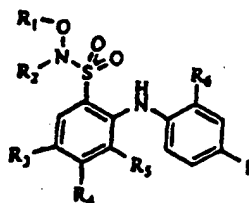


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(54) Title: SULPHOHYDROXAMIC ACIDS AND SULPHOHYDROXAMATES AND THEIR USE AS MEK INHIBITORS



(I)

(57) Abstract

Sulphohydroxamic acid diarylamines of formula (I), in which the variables are as defined in the claims, are inhibitors of MEK and are effective in the treatment of proliferative diseases, cancer, stroke, heart failure, xenograft rejection, arthritis, cystic fibrosis, hepatomegaly, cardiomegaly, Alzheimer's disease, complications of diabetes, septic shock, and viral infection.

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SULPHOHYDROXAMIC ACIDS AND SULPHOHYDROXAMATES AND THEIR USE AS MEK INHIBITORS

The invention relates to sulfohydroxamic acid diarylamines and derivatives thereof. The disclosed diarylamines are pharmacologically active.

BACKGROUND

MEK enzymes are dual specificity kinases involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis.

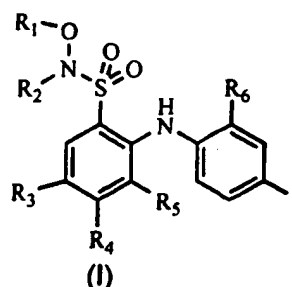
Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Defects include a change either in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade. The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK₁ and MEK₂) which then activates MAP kinase, ERK (ERK₁ and ERK₂). Activation of MAP kinase by mitogens appears to be essential for proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a

dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S218 and S222 in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y185, and a threonine residue, T183, separated by a single amino acid. This double phosphorylation activates MAP kinase at least 100-fold. Activated MAP kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than the MAP kinase, ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

SUMMARY

The invention features a compound having the formula (I) below:



5

R_1 is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, C₃₋₈ cycloalkyl, phenyl, (phenyl)C₁₋₄ alkyl, (phenyl)C₃₋₄ alkenyl, (phenyl)C₃₋₄ alkynyl, (C₃₋₈ cycloalkyl)-C₁₋₄ alkyl, (C₃₋₈ cycloalkyl)C₃₋₄ alkenyl, (C₃₋₈ cycloalkyl)C₃₋₄ alkynyl, C₃₋₈ heterocyclic radical, (C₃₋₈ heterocyclic radical)C₁₋₄ alkyl, (C₃₋₈ heterocyclic radical)C₃₋₄ alkenyl, (C₃₋₈ heterocyclic radical)C₃₋₄ alkynyl, (CH₂)₂₋₄ OR_C or (CH₂)₂₋₄ NR_CR_D. R_2 is H, C₁₋₄ alkyl, phenyl, C₃₋₆ cycloalkyl, C₃₋₆ heterocyclic radical, or (C₃₋₆ cycloalkyl) methyl. Each of R_3 and R_4 is independently selected from H, F, NO₂, Br and Cl. R_5 is selected from H and F. R_6 is H, F, Cl or CH₃. Each of R_C and R_D is independently selected from H, C₁₋₄ alkyl, C₃₋₄ alkenyl, C₃₋₄ alkynyl, C₃₋₆ cycloalkyl, and phenyl; or NR_CR_D may be a piperidino, morpholino, or N-(C₁₋₆ alkyl)piperazino ring. Each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO₂. Each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₄ alkenyl, C₃₋₄ alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO₂, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 3 substituents independently selected from halo, C₁₋₂ alkyl, hydroxyl, amino, and NO₂. The invention also includes a pharmaceutically acceptable salt or C₁₋₈ ester of a disclosed compound. For example, the disclosed alcohol compounds may form esters having the structure obtained by replacing the H of a hydroxyl group with a -C(=O)C₁₋₇ acyl group.

25

The invention also relates to a pharmaceutical composition including

(a) a compound of formula (I) and (b) a pharmaceutically-acceptable carrier.

The invention further relates to a method for treating proliferative diseases, such as cancer, restenosis, psoriasis, autoimmune disease, and atherosclerosis.

Other aspects of the invention include methods for treating MEK-related

5 (including ras-related) cancers, whether solid or hematopoietic. Examples of cancers include colorectal, cervical, breast, ovarian, brain, acute leukemia, gastric, non-small cell lung, pancreatic, and renal cancer. Further aspects of the invention include methods for treating or reducing the symptoms of xenograft (skin, cell(s), limb, organ or bone marrow transplant) rejection, osteoarthritis, 10 rheumatoid arthritis, cystic fibrosis, complications of diabetes (including diabetic retinopathy and diabetic nephropathy), hepatomegaly, cardiomegaly, stroke (such as acute focal ischemic stroke and global cerebral ischemia), heart failure, septic shock, asthma, and Alzheimer's disease. Compounds of the invention are also useful as antiviral agents for treating viral infections such as HIV, hepatitis (B) 15 virus (HBV), human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). These methods include the step of administering to a patient in need of such treatment, or suffering from such a disease or condition, a pharmaceutically-effective amount of a disclosed compound or pharmaceutical composition thereof.

20 The invention also features methods of combination therapy, such as a method for treating cancer, wherein the method further includes providing radiation therapy or chemotherapy, for example, with mitotic inhibitors such as a taxane or a vinca alkaloid. Examples of mitotic inhibitors include paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine. Other therapeutic 25 combinations include a MEK inhibitor of the invention and an anticancer agent such as cisplatin, 5-fluorouracil or 5-fluoro-2,4-(1H,3H)-pyrimidinedione (5FU), flutamide, and gemcitabine.

The chemotherapy or radiation therapy may be administered before, concurrently, or after the administration of a disclosed compound according to the 30 needs of the patient.

The invention also includes synthetic intermediates and methods disclosed herein.

Other aspects of the invention are provided in the description, examples, and claims below.

DETAILED DESCRIPTION

5 The invention features diaryl amine compounds, pharmaceutical compositions thereof, and methods of using such compounds and compositions.

 According to one aspect of the invention, the compounds are MEK inhibitors. MEK inhibition assays include the in vitro cascade assay for inhibitors of MAP kinase pathway described at column 6, line 36 to column 7, line 4 of U.S.
10 Patent Number 5,525,625 and the in vitro MEK assay at column 7, lines 4-27 of the same patent, the entire disclosure of which is incorporated by reference (see also Examples 1-3 below). A whole cell assay is described below in Example 4.

A. Terms

15 Certain terms are defined below and by their usage throughout this disclosure.

 Alkyl groups include aliphatic (i.e., hydrocarbyl or hydrocarbon radical structures containing hydrogen and carbon atoms) with a free valence. Alkyl groups are understood to include straight chain and branched structures.

20 Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, and octyl. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

 Alkyl groups can be substituted with 1, 2, 3 or more substituents which are
25 independently selected from halo (fluoro, chloro, bromo, or iodo), hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-
30 thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-dimethylaminobutyl, methoxymethyl, N-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

6

Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, and their nonaromatic counterparts. Further examples of heterocyclic radicals include

5 piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, octahydrobenzothiofuranyl, and octahydrobenzofuranyl.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other

10 enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC_{50} for MEK 1 or MEK 2 that is at least one-fiftieth ($1/50$) that of its IC_{50} for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC_{50} that is at least $1/100$, more preferably $1/500$, and even more preferably

15 $1/1000$, $1/5000$, or less than that of its IC_{50} or one or more of the above-named enzymes.

B. Compounds

One aspect of the invention features the disclosed compounds shown in

20 formula (I) in the Summary section.

Embodiments of the invention include compounds wherein: (a) R_3 is bromo or chloro; (b) R_4 is fluoro; (c) R_5 is H; (d) each of R_4 and R_5 is H; (e) each of R_4 and R_5 is fluoro; (f) R_3 is bromo; (g) R_3 is fluoro; (h) R_4 is nitro; (i) R_5 is H; (j) R_6 is chloro; (k) R_6 is methyl; (l) R_1 is H or C_{1-4} alkyl, and R_2 is H; (m) R_1 is

25 $(C_{3-6} \text{ cycloalkyl})\text{methyl}$; (n) R_1 is H; (o) R_1 is $(CH_2)_{2-4}OR_C$ or $(CH_2)_{2-4}NR_C R_D$; (p) R_6 is chloro or methyl; (q) R_6 is H; or combinations thereof.

Preferably, when R_1 , R_C , or R_D is an alkenyl or alkynyl, the double or triple bond, respectively, is not adjacent the point of attachment when the point of attachment is a heteroatom. For example, R_1 is preferably prop-2-ynyl, or but-2

30 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

Examples of compounds of formula (I) include: 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 4-fluoro-N-hydroxy-2-(4-iodo-2-

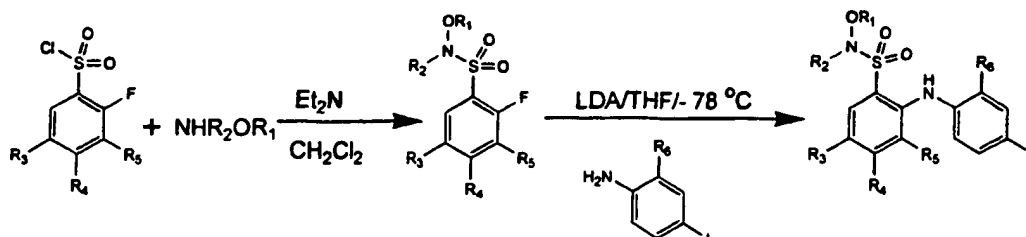
methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4,5-trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 5-bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonic acid; N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide; or N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide.

Further examples of compounds include: 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-4-nitro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzenesulfonamide; or 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzenesulfonamide.

C. Synthesis

The disclosed compounds can be synthesized according to Scheme 1 below.

5



One equivalent of appropriately substituted sulfonyl chloride is added to a solution of one equivalent of appropriately substituted hydroxylamine and excess triethylamine in CH_2Cl_2 or Et_2O and stirred for 30 minutes. The triethylamine hydrochloride precipitate is separated by filtration and discarded. If necessary, the product is further purified by chromatography on silica column. The pure 2-fluor hydroxamic or hydroxamate product is then added to a solution of appropriately substituted lithium anilide prepared by adding LDA to the aniline in THF at -78°C . After stirring at room temperature for 16 hours, the reaction mixture is poured in to $\text{Et}_2\text{O}\cdot\text{HCl}$. Any precipitated solid is separated by filtration and discarded. The filtrate is concentrated and the resulting crude product is purified on silica column to give the desired target product.

The disclosed compounds can also be made by other synthetic organic methods, as well as automated or combinatorial methods.

D. Uses

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions as provided in the Summary section, as well as diseases or conditions modulated by the MEK cascade. Examples include stroke, heart failure, osteoarthritis, rheumatoid arthritis, organ transplant rejection, and a variety of tumors such as ovarian, lung, pancreatic, brain, prostatic, and colorectal.

1. Dosage

Those skilled in the art will be able to determine, according to known methods, the appropriate dosage for a patient, taking into account factors such as age, weight, general health, the type of pain requiring treatment, and the presence of other medications. In general, an effective amount will be between 0.1 and 1000 mg/kg per day, preferably between 1 and 300 mg/kg body weight, and daily dosages will be between 10 and 5000 mg for an adult subject of normal weight. Commercially available capsules or other formulations (such as liquids and film-coated tablets) of 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

2. Formulations

Dosage unit forms include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses. Dosage unit forms can also be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants. Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption accelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.

Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens,

chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.

3. Related compounds

5 The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as salts, esters, amides, hydrates or solvated forms thereof; masked or protected forms; and racemic mixtures, or enantiomerically or optically pure forms.

Pharmaceutically acceptable salts, esters, and amides include carboxylat
10 salts (e.g., C₁₋₈ alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic), amino acid addition salts, esters, and amides which are within a reasonable benefit/risk ratio, pharmacologically effective, and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate,
15 nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium,
20 quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C₁₋₆ alkyl amines and
25 secondary di (C₁₋₆ alkyl) amines. Secondary amines include 5- or 6-membered heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C₁₋₃ alkyl primary amines, and di (C₁₋₂ alkyl)amines. Representative pharmaceutically acceptable esters of the invention include C₁₋₇
30 alkyl, C₅₋₇ cycloalkyl, phenyl, and phenyl(C₁₋₆)alkyl esters. Preferred esters include methyl esters.

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. Some of these masked or protected compounds are pharmaceutically acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

HYDROXYL PROTECTING GROUPS

Hydroxyl protecting groups include: ethers, esters, and protection for 1,2- and 1,3-diols. The ether protecting groups include: methyl, substituted methyl ethers, substituted ethyl ethers, substituted benzyl ethers, silyl ethers and conversion of silyl ethers to other functional groups.

Substituted Methyl Ethers

Substituted methyl ethers include: methoxymethyl, methylthiomethyl, *t*-butylthiomethyl, (phenyldimethylsilyl) methoxymethyl, benzyloxymethyl, *p*-ethoxybenzyloxymethyl, (4-methoxyphenoxy) methyl, guaiacolmethyl, *t*-butoxymethyl, 4-pentenylloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloro-ethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydro-pyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-ethanobenzofuran-2-yl.

Substituted Ethyl Ethers

Substituted ethyl ethers include: 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

Substituted Benzyl Ethers

Substituted benzyl ethers include: *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl,

p-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p*, *p*'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α -naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimido-phenyl)methyl, 4,4',4''-tris(levulinoyloxy-phenyl)methyl, 4,4',4''tris(benzoyloxy-phenyl)methyl, 3-(imidazol-1-ylmethyl)-bis(4',4''-dimethoxyphenyl)-methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl) xanthenyl, 9-(9-phenyl-10-oxo) anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl *S,S*-dioxido.

10 Silyl Ethers

Silyl ethers include: trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxy-phenylsilyl.

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ESTERS

Esters protecting groups include: esters, carbonates, assisted cleavage, miscellaneous esters, and sulfonates.

Esters

- 20 Examples of protective esters include: formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-*P*-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio) pentanoate, pivaloate, adamantate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, and 2,4,6-trimethylbenzoate (mesitoate).
- 25

Carbonates

- Carbonates include: methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl) ethyl, 2-(phenylsulfonyl) ethyl, 2-(triphenylphosphonio) ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl,
- 30

o-nitrobenzyl, *p*-nitrobenzyl, *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

Assisted Cleavage

- Examples of assisted cleavage protecting groups include: 2-iodobenzoate, 4-azido-butylate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl) benzoate, 2-formylbenzene-sulfonate, 2-(methylthiomethoxy) ethyl carbonate, 4-(methylthiomethoxymethyl) benzoate, and 2-(methylthiomethoxymethyl) benzoate.

Miscellaneous Esters

- In addition to the above classes, miscellaneous esters include: 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl) phenoxyacetate, 2,4-bis(1,1-dimethylpropyl) phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenate (tigloate), *o*-(methoxycarbonyl) benzoate, *p*-P-benzoate, α -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethyl-phosphorodiamidate, *N*-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate.

Sulfonates

- Protective sulfates includes: sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

PROTECTION FOR 1,2- AND 1,3-DIOLS

The protection for 1,2 and 1,3-diols group includes: cyclic acetals and ketals, cyclic ortho esters, and silyl derivatives.

Cyclic Acetals and Ketals

- Cyclic acetals and ketals include: methylene, ethylidene, 1-*t*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl) ethylidene, 2,2,2-trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

Cyclic Ortho Esters

Cyclic ortho esters include: methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidene, 1,2-dimethoxyethylidene, α -methoxybenzylidene, 1-(*N,N*-dimethylamino)ethylidene derivative, α -(*N,N*-
5 dimethylamino) benzylidene derivative, and 2-oxacyclopentylidene.

PROTECTION FOR THE CARBOXYL GROUP

ESTERS

Ester protecting groups include: esters, substituted methyl esters, 2-substituted
10 ethyl esters, substituted benzyl esters, silyl esters, activated esters, miscellaneous derivatives, and stannyl esters.

Substituted Methyl Esters

Substituted methyl esters include: 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-
15 (trimethylsilyl)ethoxy-methyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl, α -methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-phthalimidomethyl.

2-Substituted Ethyl Esters

20 2-Substituted ethyl esters include: 2,2,2-trichloroethyl, 2-haloethyl, 1-chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2(*p*-nitrophenylsulfenyl)-ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl, α -methylcinnamyl,
25 phenyl, *p*-(methylmercapto)-phenyl, and benzyl.

Substituted Benzyl Esters

Substituted benzyl esters include: triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzo-suberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethyl-
30 benzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-

dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, piperonyl, and 4-P-benzyl.

Silyl Esters

- Silyl esters include: trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, and di- *t*-butylmethylsilyl.

Miscellaneous Derivatives

Miscellaneous derivatives includes: oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group, and pentaaminocobalt(III) complex.

Stannyl Esters

Examples of stannyl esters include: triethylstannyl and tri-*n*-butylstannyl.

AMIDES AND HYDRAZIDES

- Amides include: *N,N*-dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophenanthridinyl, *o*-nitroanilides, *N*-7-nitroindolyl, *N*-8-nitro-1,2,3,4-tetrahydroquinolyl, and *p*-P-benzenesulfonamides. Hydrazides include: *N*-phenyl, *N,N'*-diisopropyl and other dialkyl hydrazides.

PROTECTION FOR THE AMINO GROUP

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CARBAMATES

Carbamates include: carbamates, substituted ethyl, assisted cleavage, photolytic cleavage, urea-type derivatives, and miscellaneous carbamates.

Carbamates

- Carbamates include: methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydro-thioxanthyl)]methyl, and 4-methoxyphenacyl.

Substituted Ethyl

- Substituted ethyl protective groups include: 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'-and 4'-

pyridyl)ethyl, 2-(*N,N*-isocyclohexylcarboxamido)-ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, connamyl, 4-nitrocinnamyl, quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, and
 5 diphenylmethyl.

Assisted Cleavage

Protection via assisted cleavage includes: 2-methylthioethyl, 2-methylsulfonyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethyl-thiophenyl, 2-phosphonioethyl,
 10 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolyl-methyl, and 2-(trifluoromethyl)-6-chromonylmethyl.

Photolytic Cleavage

Photolytic cleavage methods use groups such as: *m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl.
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Urea-Type Derivatives

Examples of urea-type derivatives include: phenothiazinyl-(10)-carbonyl derivative, *N*'-*p*-toluenesulfonylaminocarbonyl, and *N*'-phenylaminothiocarbonyl.

Miscellaneous Carbamates

In addition to the above, miscellaneous carbamates include: *t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxy-benzyl, diisopropylmethyl, 2,2-dimethoxy-carbonylvinyl, *o*-(*N,N*-dimethyl-carboxamido)-benzyl, 1,1-dimethyl-3(*N,N*-
 25 dimethylcarboxamido)propyl, 1,1-dimethyl-propynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*(*p*'-methoxyphenyl-azo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropyl-methyl, 1-methyl-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1(*p*-henylazophenyl)-ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl,
 30 *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium) benzyl, and 2,4,6-trimethylbenzyl.

AMIDES**Amides**

- Amides includes: *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trichloroacetyl,
- 5 *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridyl-carboxamide, *N*-benzoylphenylalanyl derivative, *N*-benzoyl, and *N*-*p*-phenylbenzoyl.

Assisted Cleavage

- Assisted cleavage groups include: *N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N*'-dithiobenzoyloxycarbonylamino)acetyl, *N*-3-
- 10 (*p*-hydroxyphenyl) propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine derivative, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-
- 15 oxazolin-2-one.

Cyclic Imide Derivatives

- Cyclic imide derivatives include: *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenyl-maleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyl-disilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triaza-
- 20 cyclohexan-2-one, 5-substituted 1,3-dibenzyl- 1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

SPECIAL -NH PROTECTIVE GROUPS

- 25 Protective groups for –NH include: *N*-alkyl and *N*-aryl amines, imine derivatives, enamine derivatives, and *N*-hetero atom derivatives (such as *N*-metal, *N*-N, *N*-P, *N*-Si, and *N*-S), *N*-sulfenyl, and *N*-sulfonyl.

***N*-Alkyl and *N*-Aryl Amines**

- N*-alkyl and *N*-aryl amines include: *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]-
- 30 methyl, *N*-3-acetoxypentyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl,

N-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and *N*-2-picolylamine *N*'-oxide.

Imine Derivatives

Imine derivatives include: *N*-1,1-dimethylthiomethylene, *N*-benzylidene,

- 5 *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*-(*N*',*N*'-dimethylaminomethylene), *N,N*'-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, and *N*-cyclohexylidene.

Enamine Derivative

- 10 An example of an enamine derivative is *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl).

N-Hetero Atom Derivatives

N-metal derivatives include: *N*-borane derivatives, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, and *N*-copper or *N*-zinc chelate. Examples of *N-N* derivatives include: *N*-nitro,

- 15 *N*-nitroso, and *N*-oxide. Examples of *N-P* derivatives include: *N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl.

Examples of *N*-sulfenyl derivatives include: *N*-benzenesulfenyl,

N-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl,

- 20 *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxy-benzenesulfenyl, *N*-triphenylmethylsulfenyl, and *N*-3-nitropyridinesulfenyl. *N*-sulfonyl derivatives include: *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxy-benzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzene- sulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy- 4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*- β -trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)-benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl.
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- 30

- Disclosed compounds which are masked or protected may be prodrugs, compounds metabolized or otherwise transformed *in vivo* to yield a disclosed compound, e.g., transiently during metabolism. This transformation may be a hydrolysis or oxidation which results from contact with a bodily fluid such as blood, or the action of acids, or
- 5 liver, gastrointestinal, or other enzymes.

Features of the invention are further described in the examples below.

E. EXAMPLES

SYNTHETIC EXAMPLE

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Preparation of 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide (PD 0297447)

N-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide.

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To a stirring suspension comprised of O-cyclopropylmethyl-hydroxylamine hydrochloride (5.40 g, 0.0437 mol) in dichloromethane (20 ml) at ambient temperature under a nitrogen atmosphere was added diisopropylethylamine (10.8 ml, 0.062 mol). A solution comprised of 2,3,4-trifluorobenzenesulfonyl chloride (Oakwood Products, Inc., 1.00 g, 4.34×10^{-3} mol) in dichloromethane (120 ml)

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was added dropwise to the reaction vessel containing the stirring suspension over a 12 minute period. The reaction mixture was stirred for another 12 minutes and was quenched with 10 % aqueous hydrochloric acid (140 ml). The biphasic mixture was stirred vigorously for 16 hours. The layers were separated and the organic phase was dried (MgSO_4) and concentrated to 6 ml volume. The

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concentrated solution was administered to a flash silica column (Biotage, 90 g of silica gel). Elution with dichloromethane afforded 0.8283 g of a white amorphous solid; 68 % yield; $^1\text{H-NMR}$ (400 MHz; CDCl_3 signal offset to δ 7.03; values reported are uncorrected) δ 7.50 (m, 1H), 7.10 (s, 1H), 6.95 (m, 1H), 3.59 (d, 2H, $J=7.2$ Hz), 0.80 (m, 1H), 0.31 (m, 2H), 0.02 (m, 2H); $^{19}\text{F-NMR}$ (376 MHz; CDCl_3) δ -122.65 (m, 1F), -129.37 (m, 1F), -156.20 (m, 1F); MS (APCI-) 280 (M-1, 100), 210 (55), 195 (45).

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2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide (PD 0297447).

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To a stirring solution comprised of 2-chloro-4-iodoaniline in tetrahydrofuran (10 ml) at -78°C under a nitrogen atmosphere was added a 1.0 M tetrahydrofuran solution of lithium *bis*trimethylsilylamide (6.2 ml, 6.2×10^{-3} mol) to form a green suspension. The suspension was stirred for five minutes before a

- stirring suspension comprised of lithiated *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide (prepared by adding 3.0 ml of the 1.0 M lithium *bis*trimethylsilylamide solution to a stirring solution comprised of *N*-cyclopropylmethoxy-2,3,4-trifluoro-benzenesulfonamide in 10 ml of tetrahydrofuran at -78°C under nitrogen gas) was added via canula. The cold bath was removed and the stirring suspension was stirred for one hour. The reaction mixture was quenched with 10 % aqueous hydrochloric acid (50 ml) and the biphasic mixture was concentrated *in vacuo* to an aqueous suspension that was extracted with diethyl ether (200 ml). The organic phase was dried (MgSO_4) and was concentrated *in vacuo* to afford a tan oil. The crude product was purified by flash chromatography. Elution with a gradient (hexanes-ethyl acetate 99:1 \rightarrow (2 min) 9:1 \rightarrow (25 min) 3:1 afforded 1.10 g of a white amorphous foam; 73 % yield; ^1H -NMR (400 MHz; DMSO) δ 7.69 (m, 1H), 7.59 (d, 1H, $J=1.9$ Hz), 7.34 (dd, 1H, $J=8.7, 1.9$ Hz), 7.27 (s, 1H), 7.00 (s, 1H), 6.95 (m, 1H), 6.43 (dd, 1H, $J=8.7, 5.8$ Hz), 3.52 (d, 2H, $J=7.5$ Hz), 0.74 (m, 1H), 0.34 (m, 2H), 0.02 (m, 2H); ^{19}F -NMR (376 MHz; CDCl_3) δ -124.76 (m, 1F), -136.69 (d, 1F, $J=18.3$ Hz); MS (APCI+) 515 (M+1, 100); (APCI-) 513 (M-1, 50), 443 (73), 428 (100); IR (KBr) 1491 cm^{-1} ; Anal. Calcd/found for $\text{C}_{16}\text{H}_{14}\text{ClF}_2\text{IN}_2\text{O}_3\text{S}$ C, 37.34/36.54; H, 2.74/2.71; N, 5.44/5.15; F, 7.38/7.57.
- The APK IC_{50} for PD 0297447 is $0.965\text{ }\mu\text{M}$.

BIOLOGICAL EXAMPLES

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EXAMPLE 1

Cascade assay for inhibitors of the MAP kinase pathway

- Incorporation of ^{32}P into myelin basic protein (MBP) is assayed in the presence of a glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) and a glutathione S-transferase fusion protein containing p45MEK (GST-MEK). The assay solution contains 20 mM HEPES, pH 7.4, 10 mM MgCl_2 , 1 mM MnCl_2 , 1 mM EGTA, $50\text{ }\mu\text{M}$ $[\gamma\text{-}^{32}\text{P}]\text{ATP}$, $10\text{ }\mu\text{g}$ GST-MEK, $0.5\text{ }\mu\text{g}$ GST-MAPK and $40\text{ }\mu\text{g}$ MBP in a final volume of $100\text{ }\mu\text{L}$. Reactions are stopped

after 20 minutes by addition of trichloroacetic acid and filtered through a GF/C filter mat. ^{32}P retained on the filter mat is determined using a 120S Betaplate. Compounds are assessed at 10 μM for ability to inhibit incorporation of ^{32}P .

- To ascertain whether compounds are inhibiting GST-MEK or GST MAPK, two additional protocols are employed. In the first protocol, compounds are added to tubes containing GST-MEK, followed by addition of GST-MAPK, MBP and $[\gamma\text{-}^{32}\text{P}]\text{ATP}$. In the second protocol, compounds are added to tubes containing both GST-MEK and GST-MAPK, followed by MBP and $[\gamma\text{-}^{32}\text{P}]\text{ATP}$.

- Compounds that show activity in both protocols are scored as MAPK inhibitors, while compounds showing activity in only the first protocol are scored as MEK inhibitors.

EXAMPLE 2

In vitro MAP kinase assay

- Inhibitory activity can be confirmed in direct assays. For MAP kinase, 1 μg GST-MAPK is incubated with 40 μg MBP for 15 minutes at 30°C in a final volume of 50 μL containing 50 mM Tris (pH 7.5), 10 μM MgCl_2 , 2 μM EGTA, and 10 μM $[\gamma\text{-}^{32}\text{P}]\text{ATP}$. The reaction is stopped by addition of Laemmli SDS sample buffer and phosphorylated MBP resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into MBP is determined by both autoradiography, and scintillation counting of excised bands.

EXAMPLE 3

In vitro MEK assay

- For evaluation of direct MEK activity, 10 μg GST-MEK₁ is incubated with 5 μg of a glutathione S-transferase fusion protein containing p44MAP kinase with a lysine to alanine mutation at position 71 (GST-MAPK-KA). This mutation eliminates kinase activity of MAPK, so only kinase activity attributed to the added MEK remains. Incubations are 15 minutes at 30°C in a final volume of 50 μL containing 50 mM Tris (pH 7.5), 10 μM MgCl_2 , 2 μM EGTA, and 10 μM $[\gamma\text{-}^{32}\text{P}]\text{ATP}$. The reaction is stopped by addition of Laemmli SDS sample buffer.

Phosphorylated GST-MAPK-KA is resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into GST-MAPK-KA is determined by autoradiography, and subsequent scintillation counting of excised bands. Additionally, an artificially activated MEK containing serine to glutamate mutations at positions 218 and 222 (GST-MEK-2E) is used. When these two sites are phosphorylated, MEK activity is increased. Phosphorylation of these sites can be mimicked by mutation of the serine residues to glutamate. For this assay, 5 µg GST-MEK-2E is incubated with 5 µg GST-MAPK-KA for 15 minutes at 30°C in the same reaction buffer as described above. Reactions are terminated and analyzed as above.

EXAMPLE 4

Whole cell MAP kinase assay

To determine if compounds block activation of MAP kinase in whole cells, the following protocol is used. Cells are plated in multi-well plates and grown to confluence. Cells are serum-deprived overnight. Cells are exposed to the desired concentrations of compound or vehicle (DMSO) for 30 minutes, followed by addition of a growth factor, for example, PDGF (100 ng/mL). After a 5-minute treatment with the growth factor, cells are washed with PBS, and lysed in a buffer consisting of 70 mM NaCl, 10 mM HEPES (pH 7.4), 50 mM glycerol phosphate, and 1% Triton X-100. Lysates are clarified by centrifugation at 13,000 x g for 10 minutes. Five micrograms of the resulting supernatants are incubated with 10 µg microtubule associated protein-2 (Map2) for 15 minutes at 30°C in a final volume of 25 µL containing 50 mM Tris (pH 7.4), 10 mM MgCl₂, 2 mM EGTA and 30 µM [γ-³²P]ATP. Reactions are terminated by addition of Laemmli sample buffer. Phosphorylated Map2 is resolved on 7.5% acrylamide gels and incorporated radioactivity is determined by scintillation counting of excised bands.

EXAMPLE 5

Monolayer growth

Cells are plated into multi-well plates at 10 to 20,000 cells/mL. Forty-eight
5 hours after seeding, test compounds are added to the cell growth medium and
incubation is continued for 2 additional days. Cells are then removed from the
wells by incubation with trypsin and enumerated with a Coulter counter.

EXAMPLE 6

10 Growth in soft-agar

Cells are seeded into 35-mm dishes at 5 to 10,000 cells/dish using growth
medium containing 0.3% agar. After chilling to solidify the agar, cells are
transferred to a 37°C incubator. After 7 to 10 days' growth, visible colonies are
manually enumerated with the aid of a dissecting microscope.

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EXAMPLE 7

Collagen-Induced Arthritis in Mice

Type II collagen-induced arthritis (CIA) in mice is an experimental model of
arthritis that has a number of pathologic, immunologic, and genetic features in
20 common with rheumatoid arthritis. The disease is induced by immunization of
DBA/1 mice with 100 µg type II collagen, which is a major component of joint
cartilage, delivered intradermally in Freund's complete adjuvant. The disease
susceptibility is regulated by the class II MHC gene locus, which is analogous to
the association of rheumatoid arthritis with HLA-DR4.

25 A progressive and inflammatory arthritis develops in the majority of mice
immunized, characterized by paw width increases of up to 100%. A test
compound is administered to mice in a range of amounts, such as 20, 60, 100,
and 200 mg/kg body weight/day. The duration of the test can be several weeks
to a few months, such as 40, 60, or 80 days. A clinical scoring index is used to
30 assess disease progression from erythema and edema (stage 1), joint distortion
(stage 2), to joint ankylosis (stage 3). The disease is variable in that it can affect
on or all paws in an animal, resulting in a total possible score of 12 for each

mouse. Histopathology of an arthritic joint reveals synovitis, pannus formation, and cartilage and bone erosions. All mouse strains that are susceptible to CIA are high antibody responders to type II collagen, and there is a marked cellular response to CII.

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EXAMPLE 8

SCW-induced monoarticular arthritis

Arthritis is induced as described by Schwab, *et al.*, *Infection and Immunity*, 59:4436-4442 (1991) with minor modifications. Rats receive 6 µg sonicated SCW [in 10 µl Dulbecco's PBS (DPBS)] by an intraarticular injection into the right tibiotalar joint on day 0. On day 21, the DTH is initiated with 100 µg of SCW (250 µl) administered i.v. For oral compound studies, compounds are suspended in vehicle (0.5% hydroxypropyl-methylcellulose/0.2% Tween 80), sonicated, and administered twice daily (10 ml/kg volume) beginning 1 hr prior to reactivation with SCW. Compounds are administered in amounts between 10 and 500 mg/kg body weight/day, such as 20, 30, 60, 100, 200, and 300 mg/kg/day. Edema measurements are obtained by determining the baseline volumes of the sensitized hindpaw before reactivation on day 21, and comparing them with volumes at subsequent time points such as day 22, 23, 24, and 25. Paw volume is determined by mercury plethysmography.

EXAMPLE 9

Mouse ear-heart transplant model

Fey, T.A. *et al.* describe methods for transplanting split-heart neonatal cardiac grafts into the ear pinna of mice and rats (*J. Pharm. and Toxic. Meth.* 39:9-17 (1998)). Compounds are dissolved in solutions containing combinations of absolute ethanol, 0.2% hydroxypropyl methylcellulose in water, propylene glycol, cremophor, and dextrose, or other solvent or suspending vehicle. Mice are dosed orally or intraperitoneally once, twice or three times daily from the day of transplant (day 0) through day 13 or until grafts have been rejected. Rats are dosed once, twice, or three times daily from day 0 through day 13. Each animal

is anesthetized and an incision is made at the base of the recipient ear, cutting only the dorsal epidermis and dermis. The incision is spread open and down to the cartilage parallel to the head, and sufficiently wide to accommodate the appropriate tunneling for a rat or insertion tool for a mouse. A neonatal mouse or
5 rat pup less than 60 hours old is anesthetized and cervically dislocated. The heart is removed from the chest, rinsed with saline, bisected longitudinally with a scalpel, and rinsed with sterile saline. The donor heart fragment is placed into the preformed tunnel with the insertion tool and air or residual fluid is gently expressed from the tunnel with light pressure. No suturing, adhesive bonding,
10 bandaging, or treatment with antibiotics is required.

Implants are examined at 10-20-fold magnification with a stereoscopic dissecting microscope without anesthesia. Recipients whose grafts are not visibly beating may be anesthetized and evaluated for the presence of electrical activity using Grass E-2 platinum subdermal pin microelectrodes placed either in
15 the pinna or directly into the graft and a tachograph. Implants can be examined 1-4 times a day for 10, 20, 30 or more days. The ability of a test compound to ameliorate symptoms of transplant rejection can be compared with a control compound such as cyclosporine, tacrolimus, or orally-administered leflunomide.

20 EXAMPLE 10

Murine ovalbumin-induced eosinophilia

Female C57BL/6 mice are obtained from the Jackson Laboratory (Bar Harbor, ME). All animals are given food and water ad libitum. Mice are sensitized
25 with a single i.p. injection of OVA (grade V, Sigma Chemical Company, St. Louis, MO) adsorbed to alum, (10 µg OVA + 9 mg alum in 200 µl saline) or vehicle control, (9 mg alum in 200 µl saline) on day 0. On day 14, the mice are challenged with a 12-minute inhalation of an aerosol consisting of 1.5% OVA (weight/volume) in saline produced by a nebulizer (small particle generator,
30 model SPAG-2; ICN Pharmaceuticals, Costa Mesa, CA). Groups of eight mice are dosed with oral vehicle (0.5% hydroxypropylmethylcellulose / 0.25% TWEEN-80), or a test compound at 10, 30, or 100 mg/kg in oral vehicle, 200 µl per mouse

p.o. Dosing is performed once per day starting on day 7 or day 13, and extending through day 16.

For determination of pulmonary eosinophilia, three days after the first OVA aerosol challenge (day 17), the mice are anesthetized with an i.p. injection of anesthetic (Ketamine/Acepromazine/Xylazine), and the tracheae is exposed and cannulated. The lungs and upper airways are lavaged twice with 0.5 ml of cold PBS. A portion (200 μ l) of the bronchoalveolar lavage (BAL) fluid is enumerated using a Coulter counter Model ZB1 (Coulter Electronics, Hialeah, FL). The remaining BAL fluid is then centrifuged at 300 x g for five minutes, and the cells are resuspended in 1 ml of HBSS (Gibco BRL) containing 0.5% fetal calf serum (HyClone) and 10 mM HEPES (Gibco BRL). The cell suspension is centrifuged in a cytospin (Shandon Southern Instruments, Sewickley, PA) and stained by Diff Quick (American Scientific Products, McGraw Park, IL) to differentiate BAL leukocytes into neutrophil, eosinophil, monocyte or lymphocyte subsets. The number of eosinophils in the BAL fluid is determined by multiplying the percentage of eosinophils by the total cell count.

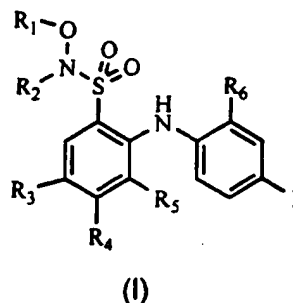
F. OTHER EMBODIMENTS

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

CLAIMS

1. A compound of formula (I):



5

- R_1 is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, C₃₋₈ cycloalkyl, phenyl, (phenyl)C₁₋₄ alkyl, (phenyl)C₃₋₄ alkenyl, (phenyl)C₃₋₄ alkynyl, (C₃₋₈ cycloalkyl)-
- 10 C₁₋₄ alkyl, (C₃₋₈ cycloalkyl)C₃₋₄ alkenyl, (C₃₋₈ cycloalkyl)C₃₋₄ alkynyl, C₃₋₈ heterocyclic radical, (C₃₋₈ heterocyclic radical)C₁₋₄ alkyl, (C₃₋₈ heterocyclic radical)C₃₋₄ alkenyl, (C₃₋₈ heterocyclic radical)C₃₋₄ alkynyl, (CH₂)₂₋₄ OR_C or (CH₂)₂₋₄ NR_CR_D;

- 15 R_2 is H, C₁₋₄ alkyl, phenyl, C₃₋₆ cycloalkyl, C₃₋₆ heterocyclic radical, or (C₃₋₆ cycloalkyl) methyl;

each of R_3 and R_4 is independently selected from H, F, NO₂, Br and Cl;

- 20 R_5 is selected from H and F;

R_6 is H, F, Cl or CH₃;

- each of R_C and R_D is independently selected from H, C₁₋₄ alkyl, C₃₋₄ alkenyl, C₃₋₄ alkynyl, C₃₋₆ cycloalkyl, and phenyl; or NR_CR_D may be a piperidino, morpholino, or N-(C₁₋₆ alkyl)piperazino ring;
- 25

wherein each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO₂; and

- 5 wherein each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₄ alkenyl, C₃₋₄ alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO₂, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected
10 from halo, C₁₋₂ alkyl, hydroxyl, amino, and NO₂;

or a pharmaceutically acceptable salt or C₁₋₈ ester thereof.

- 15 2. A compound of claim 1, wherein R₃ is bromo or chloro.
3. A compound of claim 1, wherein R₄ is fluoro.
4. A compound of claim 1, wherein R₅ is H.
- 20 5. A compound of claim 4, wherein each of R₄ and R₅ is H.
6. A compound of claim 1, wherein each of R₄ and R₅ is fluoro.
7. A compound of claim 6, wherein R₃ is bromo.
- 25 8. A compound of claim 6, wherein R₃ is fluoro.
9. A compound of claim 1, wherein R₄ is nitro.
- 30 10. A compound of claim 8, wherein R₅ is H.
11. A compound of claim 1, wherein R₆ is chloro.

5

12. A compound of claim 1, wherein R_6 is methyl.

13. A compound of claim 1, wherein R_1 is H or C_{1-4} alkyl, and R_2 is H.

14. A compound of claim 1, wherein R_1 is $(C_{3-6}$ cycloalkyl)methyl.

15. A compound of claim 1, wherein R_1 is H.

10 16. A compound of claim 1, wherein R_1 is $(CH_2)_{2-4}OR_C$ or $(CH_2)_{2-4}NR_C R_D$.

17. A compound of claim 1, having the structure: 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 4-fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 3,4,5-trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; N-cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonic acid; 5-bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 5-bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide; 2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonic acid; N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide; or N-cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzenesulfonamide.

30

18. A compound of claim 1, having the structure: 2-(2-chloro-4-iodo-phenylamino)-4-fluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-4-

- fluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzenesulfonic acid; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzenesulfonamide; 5-bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzenesulfonamide; 2-(2-chloro-4-iodo-phenylamino)-4-nitro-benzenesulfonic acid; 2-(2-chloro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzenesulfonamide; or 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzenesulfonamide.

19. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically-acceptable carrier.

20. A method for treating a proliferative disease, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

21. A method of claim 20 wherein said proliferative disease is selected from psoriasis, restenosis, autoimmune disease, and atherosclerosis.

22. A method for treating cancer, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

23. A method of claim 22, wherein said cancer is MEK-related.

24. A method of claim 22, wherein said cancer is brain, breast, lung, ovarian, pancreatic, prostatic, renal, or colorectal cancer.
- 5 25. A method for treating, or ameliorating the sequelae of, a stroke, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.
- 10 26. A method for treating, or ameliorating the sequelae of, heart failure, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.
- 15 27. A method for treating or reducing the symptoms of xenograft rejection, said method comprising administering to an organ transplant, limb transplant, skin transplant, cell(s) transplant, or bone marrow transplant patient a pharmaceutically-effective amount of a composition comprising a compound of claim 1.
- 20 28. A method for treating osteoarthritis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.
- 25 29. A method for treating rheumatoid arthritis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.
- 30 30. A method for treating cystic fibrosis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

31. A method for treating hepatomegaly, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

5 32. A method for treating cardiomegaly, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

10 33. A method for treating Alzheimer's disease, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

15 34. A method for treating a complication of diabetes, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

20 35. A method for treating septic shock, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

25 36. A method for treating a viral infection, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

37. A method of claim 36, wherein said viral infection is an infection of HIV.

30 38. A method for treating cancer, said method comprising (a) administering to a patient in need of such treatment, a pharmaceutically-effective amount of a composition comprising a compound of claim 1; and (b) administering a therapy selected from radiation therapy and chemotherapy.

39. A method of claim 38, wherein said chemotherapy comprises a mitotic inhibitor.

5 40. A method of claim 39, wherein said mitotic inhibitor is selected from paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine.

10

INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/US 99/30417

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/39 A61K31/18 A61P5/48 A61P17/06 A61P19/02
A61P25/28 A61P31/18 A61P35/00 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 37881 A (WARNER LAMBERT) 3 September 1998 (1998-09-03) page 3 -page 4	1-40
A	US 5 525 625 A (A.J. BRIDGES, ET AL.) 11 June 1996 (1996-06-11) cited in the application the whole document	1-40

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

12 May 2000

Date of mailing of the international search report

26/05/2000

Name and mailing address of the ISA

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Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 30417

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20-39
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 20-39
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Initial International Application No

PCT/US 99/30417

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9837881 A	03-09-1998	AU 5610398 A ZA 9801578 A	18-09-1998 02-09-1998
US 5525625 A	11-06-1996	AT 181913 T AU 690400 B AU 4245696 A CA 2208075 A DE 69510696 D DE 69510696 T EP 0805807 A ES 2137554 T GR 3031295 T JP 10512878 T NZ 297320 A WO 9622985 A ZA 9600528 A	15-07-1999 23-04-1998 14-08-1996 01-08-1996 12-08-1999 23-12-1999 12-11-1997 16-12-1999 31-12-1999 08-12-1998 28-05-1999 01-08-1996 15-08-1996